

**REMARKS**

Reconsideration of this application is respectfully requested.

Claims 9, 25-27 and 51-53 have been amended. Upon entry of this amendment, the pending claims will remain claims 1-53.

Support for the amendment to claim 9 may be found in the present specification at page 5, lines 17-21.

Claims 25-27 and 51-53 have been amended to change the abbreviation "NCA" to "N-carboxylic anhydride".

For the reasons given on page 2 of the Official Action, the disclosure is objected to. In particular, it is stated that the specification, e.g., at page 5, line 34, is "replete" with typographical errors.

This objection is respectfully traversed.

It is noted that the format of the present specification is basically justified. Accordingly, the amount of space between particular words varies from line-to-line.

In line 34 of page 5, a small space is observable (1) between "The" and "preferred", (2) between "preferred" and "halogenated", and (3) between "halogenated" and "hydrocarbons". In view of the justified format of the present specification, there is no typographical error on page 5, line 34.

Applicants disagree that the present specification is "replete" with typographical errors. Similar to page 5, line 34, there are other lines, such as at page 2, line 28 and at page

5, line 1, where words are somewhat compressed together. However, correction of these lines would not appear to require correction.

Attached hereto is an enlarged version of a portion of page 5 of the present specification. This enlargement shows spaces between “The”, “preferred”, “halogenated” and “hydrocarbons”.

Accordingly, the objection to the specification should be withdrawn.

For the reasons given on pages 2 and 3 of the Official Action, claims 1-53 are rejected under 35 USC 112, second paragraph.

This rejection is traversed and, in part, obviated by the foregoing amendments.

Claims 1-4, 9-21, 24, 25, 27-30, 35-49, 51 and 53 are not indefinite, because “good solvent” is a well known and commonly used term of art, which is known to those of ordinary skill in the art.

In support of applicants' position, enclosed herewith are copies of pages 620 and 765 of ENCYCLOPEDIA CHIMICA (Published by Kyoritsu Shuppan, on January 15, 1964).

Translations of pertinent passages in these pages appear below.

The translation of page 765, right column, lines 6 to 7:

Good solvent (“Ryo yobai” in Japanese) [English: good solvent; German: gutes Lösungsmittel]-See “bad solvent”)

The translation of page 620, left column, lines 16-35:

Bad solvent (Hin yobai” in Japanese) [English: bad solvent, German: Schlechtes

Lösungsmittel] “bad solvent” means a solvent having only a low capacity to dissolve a solute. On the contrary, a solvent having a large capacity to dissolve a solute is called “good solvent”. It becomes very difficult to dissolve a solute when a mutual energy between solvent molecules is very strong and an arithmetic average of mutual energy between solute molecules and between solvent molecules is markedly higher than that between solute and solvent molecules. In such a case, the solvent is a bad solvent. When the solute is a liquid form, two-phase separation is occurred in such a solvent (See “mutual solubility”), and when the solute is a solid form, the solid shows only a slight solubility. In a bad solvent, linear polymer molecules are dissolved in a state of thready ball, but in a good solvent, the molecules are dissolved in a widely spread state. In the case of purifying a solute or of separating a polymer molecule, it is commonly carried out that a solute or a polymer is dissolved in a good solvent, and then mixing the solution with a bad solvent to recrystallize or precipitate the solute.

Accordingly, one skilled in the art would know what is meant by “good solvent”, especially as this term is used in the context of the present specification.

On page three of the Official Action, it is stated that the specification only specifies that a good solvent does not cause adverse effects. No particular passage of the specification is cited to support this statement.

In the event that the objection to “good solvent” is not withdrawn, it is respectfully requested that a particular passage of the present specification is cited to support the

contention that the present specification specifies that a good solvent does not cause adverse effects.

Applicants respectfully disagree that claim 4 does not further limit claim 3.

Claim 3 recites that a temperature range is -30 to 50 °C. On the other hand, claim 4, which depends on claim 3, recites that a temperature range is -20 to 45 °C. Since the range claimed in claim 4 is fully encompassed within the range claimed in claim 3, claim 4 does not fail to limit claim 3.

The objection to the recitation of “NCA” in claims 25-27 and 51-53 has been obviated by the foregoing amendments to these claims, whereby these claims have been reworded to recite “N-carboxylic anhydride”, instead of “NCA”.

Accordingly, the rejections under 35 USC 112 should be withdrawn.

For the reasons given on pages 3-6 of the Official Action, claims 1-5, 25, 28-31, 42, 43 and 49 (but not claims 6-24, 26, 27, 32-41, 44-48, and 50-53) are rejected under 35 USC 103(a) over the disclosure of the Youssefyeh et al U.S. Patent No. 4,831,184.

This rejection is respectfully traversed.

The present invention relates to a crystallizing method of N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine N-carboxylic anhydride. According to claim 2, one aspect of the present invention is a method comprising preparing a solution of previously synthesized crude NCA (N-carboxylic anhydride) in a good solvent, and then adding the solution into an aliphatic hydrocarbon solvent to give crystallized NCA.

According to claim 28, another aspect of the present invention is a method comprising adding an aliphatic hydrocarbon solvent into the solution of NCA in a good solvent to give crystallized NCA. In both crystallization methods, two different solvents, a good solvent and an aliphatic solvent, are used, and both methods comprise a step of adding either NCA solution in good solvent or an aliphatic solvent into the other. As a result, it is possible to obtain NCA with high purity and high yield.

On the other hand, the method disclosed in USP 4,831,184 (hereinafter, referred to as "US '184") is a synthesizing method of NCA. Example 5, B. US '184 discloses synthesis of NCA by reacting N-[1 (S)-ethoxycarbonyl-3-phenylpropyl]-(S)-alanine with phosgene in dry THF. Then NCA is obtained by heating the mixture to a gentle reflux and evaporating solvents. In US '184, dry THF and toluene are used as solvents to dissolve the raw materials or as reaction solvents, but not as crystallization solvents. It is only after evaporation of the solvents that NCA is obtained.

In the Official Action, it is stated that the present invention is *prima facie* obvious because the present invention is only a rearrangement of the steps described in US '184 without any unexpected results. However, the present invention is not a rearrangement of US '184. Differences are mentioned below.

First, the present invention relates to a crystallizing method to recover pure NCA from crude NCA. Therefore, the present invention differs from US '184, for US '184 merely discloses a method for synthesizing NCA. The method disclosed in Example 5, B

of US '184 corresponds to Preparation Example on page 17, line 33 to page 18, line 12 of the instant specification. The subject matter of the present invention consists in a purification process after these synthesizing processes. On the other hand, US '184 describes that "The N-carboxyanhydride was used directly in the next reaction without further purification".on column 11, lines 1-2. Thus, the present purification method of NCA is not disclosed at all.

Next, a feature of the present invention consists in the use of a good solvent and an aliphatic hydrocarbon solvent. US '184 discloses use of toluene, which is an aromatic solvent, but an aliphatic hydrocarbon solvent is not used in US '184. In addition, the crystallization of the present invention is carried out in the presence of a solvent, but in US '184, crystallized NCA is not produced in the presence of a solvent. Thus, use of an aliphatic solvent is not obvious from US '184.

Furthermore, another feature of the present invention consists in the crystallization process carried out in the presence of solvents. On the contrary, evaporation of solvents is needed for crystallization for US '184 to obtain the objective NCA. There are no teachings or suggestions in US '184 about the crystallization method of the present invention, and therefore the present invention is not obvious from US '184.

In addition, unexpected effects are obtained as a result of the present invention. According to the disclosure on page 34, lines 27 to 34 of the instant specification, the present invention provides a high-purity product as crystals with a recovery rate of not less than 90% and with large particle diameter. In addition, NCA can be recovered with its

extremely high optical purity being well retained. These results are not expected from the disclosure of US '184.

Consequently, the present invention is not obvious from US '184.

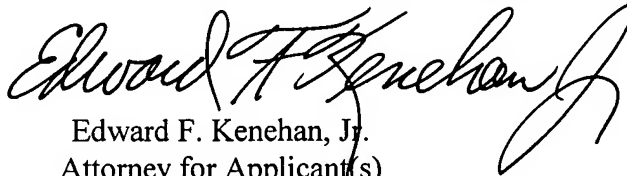
Accordingly, the rejection under 35 USC 103 should be withdrawn.

Allowance is requested.

In the event that this paper is not timely filed, Applicant respectfully petition for an appropriate extension of time. The fees for such an extension or any other fees that may be due with respect to this paper may be charged to Deposit Account No. 50-2866.

Respectfully submitted,

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EFK/jli

Enclosures: copy of Encyclopedia Chemical, pages 620 and 765  
enlarged version of a portion of page 5 of the present specification

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